Iodine deficiency is a major cause of goiter development. However, there are many other causes that can lead to an increase or change in the consistency of the thyroid gland. In order to be able to come to an unambiguous assessment, differential diagnostic skills are essential. Therefore, the following article may help you learn more about the etiology and differential diagnosis of goiter.

Definition of Goiter

Goiter as a symptom
Goiter is a symptom that describes the **enlargement of the thyroid gland**. The term “goiter” is purely descriptive in nature and thus reveals nothing about the pathogenesis or the functional status of the thyroid gland. Goiter may be associated with normal functioning thyroid gland (euthyroid goiter), overactive thyroid gland (toxic goiter), or underactive thyroid gland (hypothyroid goiter).

Goiters may extend into the retrosternal space, with or without substantial anterior enlargement. Because of the anatomic relationship of the thyroid gland to the trachea, larynx, superior and inferior laryngeal nerves, and esophagus, abnormal growth may cause a variety of compressive syndromes.

**What does an enlarged thyroid mean?**

An enlarged thyroid also known as goiter refers to the increase in the size of the thyroid gland. The thyroid is an endocrine organ located on the anterior aspect of the neck region as two butterfly-shaped lobes on each side of the trachea each measuring 4-6 cm by 1.2-1.8 cm and a central isthmus that measure 4-5 mm in diameter. An increase in any of the above measurements refers to thyroid enlargement that may be asymptomatic or present with features of mass effect.

**Epidemiology of Goiter**

**Goiter — Common findings**

The WHO estimates that two billion people, including 285 million school-age children still have iodine deficiency. Goiter is endemic in areas where daily iodine intake is lower than 50 μg and congenital hypothyroidism is risked when the daily intake further falls to 25 μg. The prevalence of goiter in areas of severe iodine deficiency can be as high as 80%. Overall, women are more often affected than men.

**Classification of Goiter**
Classification of goiter-size stages by WHO

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No goiter</td>
</tr>
<tr>
<td>Ia</td>
<td>Palpable goiter, not visible when bending the head back, solitary nodule</td>
</tr>
<tr>
<td>Ib</td>
<td>Palpable goiter, only visible when bending the head back</td>
</tr>
<tr>
<td>II</td>
<td>Visible and palpable goiter even without the reclining head</td>
</tr>
<tr>
<td>III</td>
<td>Goiter visible at a distance, with obstruction of the trachea and esophagus or spreading behind the sternum</td>
</tr>
</tbody>
</table>

Classification of goiter after thyroid hormone function

<table>
<thead>
<tr>
<th>Condition</th>
<th>Thyroid hormone level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Euthyroid</strong></td>
<td>Thyroid hormone level in the normal range</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Decreased thyroid hormone level</td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td>Increased thyroid hormone level</td>
</tr>
</tbody>
</table>

Etiology and Pathogenesis of Goiter

Causes of goiter

A deficiency in thyroid hormone synthesis or intake leads to increased thyroid-stimulating hormone (TSH) production. Increased TSH causes increased cellularity and hyperplasia of the thyroid gland in an attempt to normalize thyroid hormone levels. If this process is sustained, a goiter is established.

The most common cause in industrialized countries is an **endemic iodine deficiency** (alimentary iodine deficiency). In countries where iodine is routinely added to table salt and other foods, a lack of dietary iodine is not the main cause, other possible causes are responsible:

**Inflammation**
Autoimmune disorders of the thyroid (Graves' disease, Hashimoto’s thyroiditis)
Medications (phenytoin, lithium, anti-thyroid drugs, carbimazole)

Thyroid autonomy

Thyroid tumors
- Neoplastic production of TSH
  - Acromegaly
- Iodine failed use

Symptoms of Goiter

An enlarged thyroid gland may present with:
- Features of mass effect such as discomfort to the enlarging mass, difficulty in breathing once the airway is compressed and difficulty in swallowing that arises from compression of the esophagus.
- Features of hyperthyroidism in toxic goiters which mainly arise from activation of the autonomic nervous system by the hormones from the glands. The features include fast heartbeat, increased sweating, anxiety, heavy menstrual bleeding, tremors, and heat intolerance.
- Features of hypothyroidism in non-functional goiters which occur due to deficiency of the hormones. They include a slow heart rate, weight gain despite poor appetite, lethargy, scanty menstrual flow, infertility, and cold intolerance.
- Features of invasiveness if the enlargement is cancerous which include weight loss due to increased basal metabolic rate and hoarseness of voice due to the encroachment of the recurrent laryngeal nerve by the tumor.
- Features of inflammation if the enlargement is infective or autoimmune in nature such as pain in the neck.
- Hemorrhage and/or necrosis may be a result of traumatic injury to the organ.

Non-specific symptoms of goiter

Most goiters are asymptomatic. A visible thyroid enlargement can only be seen from a volume of about 40 ml. The enlargement of the thyroid gland can be accompanied by mechanical compression of surrounding organs (tracheal and/or esophagus compression).

The extent to which goiter is symptomatic essentially depends on the location. In the case of retrosternal or retrotracheal growth, it may restrict the larynx and/or trachea in their anatomical position so much that dysphagia, dyspnea and hoarseness may occur.

In the case of esophagus compression, the patient may complain of globus or pressure sensation in the throat, as well as problems with swallowing. It may accompany pain in thyroid region and cough.

<table>
<thead>
<tr>
<th>Common Symptom</th>
<th>Restricted Organ/Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stridor, hoarseness, dyspnea</td>
<td>Compression of the trachea</td>
</tr>
<tr>
<td>Dysphagia, globus sensation</td>
<td>Compression of the larynx and/or trachea</td>
</tr>
<tr>
<td>Inflow congestion</td>
<td>Compression of the neck veins</td>
</tr>
</tbody>
</table>
Specific symptoms of goiter

Clear indications of the possible presence of goiter are diffuse or nodular enlargement of the thyroid tissue.

Diagnosis of Goiter

First signs of goiter

Avoiding necklaces, turtlenecks or an increase in the collar size can be regarded as the first indication of the presence of goiter.

Anamnestic response in suspected goiter

A detailed medical history may provide the first evidence for the presence of a goiter. What should be questioned in detail:

- Duration and progression of thyroid enlargement
- Possible exposure of the head and neck region
- Recently occurred hoarseness
- Hormonal changes (puberty, pregnancy, menopause)
- Taking medications
- Iodine intake
- Family history

Goiter clinic

You should start with a physical examination i.e. inspection of the enlargement. At the beginning of a first-glance examination, you may work with the goiter-size stages classification provided by WHO (see above). You should examine the thyroid gland with a straight back and a bowed head. You should pay attention to a possible visible enlargement as well as nodes and signs of upper inflow congestion.

Palpation is the second step of examination. During the physical examination, it allows making further judgment in regards to the extension of a goiter and other clinical signs of malignancy. Important points in this case are:

- Mobility of tissues;
- Any enlargement of tissues;
- Uniform consistency of tissues;
- Possibly, to palpate lumps and nodes;
- Buzz under the palpating fingers;
- Increased sensitivity to touch;
- Tenderness;
- Lymph node enlargement.

In addition to palpation, you may also use auscultation. If there is an increased blood supply to the thyroid tissue, this can be perceived as audible buzz auscultation. If it happens, you should think of the presence of hyperthyroidism.
Further diagnosis in the presence of goiter

With an anamnestic history and physical examination of the suspected goiter, the following examinations should take place:

- Ultrasonography of the thyroid gland for accurate detection of thyroid enlargement and morphological differentiation of the various forms of goiter.
- Determination of TSH, TRH, free T3 and free T4 for the evaluation of thyroid function.

With a multinodular or nodular goiter, the following questions are to be answered: Is a thyroid autonomy available? Is it a benign change or a tumor, if the tissues have changed? In order to get a differentiated answer to these questions, the following further diagnostic modalities should be considered:

- Laboratory tests;
- Scintigraphy;
- Unenhanced computed tomography;
- Magnetic Resonance Imaging;
- Fine-needle biopsy.

Differential Diagnosis of Goiter

Various forms of goiter

The diagnosis of goiter initially leads to the differentiation into **diffuse** and **nodular goiter**.
<table>
<thead>
<tr>
<th>Goiter Form</th>
<th>Description</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid goiter (bland goiter)</td>
<td>Benign, with euthyroid serum levels and normal thyroid function.</td>
<td>With normal serum levels without direct clinical significance.</td>
</tr>
<tr>
<td>Euthyroid nodular goiter/ multinodular goiter</td>
<td>Nodular goiter, at the beginning mostly euthyroid; in the further course, there are signs of hyperthyroidism.</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Diffuse goiter (struma parenchymatosa)</td>
<td>Not definable enlargement of the thyroid gland with uniform growth; common cause: iodine deficiency.</td>
<td>Puberty goiter, Graves' disease</td>
</tr>
<tr>
<td>Basedow's goiter</td>
<td>Diffuse parenchymal goiter with abundant vascular development, liquid colloid and epithelium tumor.</td>
<td>Graves' disease</td>
</tr>
<tr>
<td>Lymphatic goiter Hashimoto (struma lymphomatosa Hashimoto)</td>
<td>Over the years, increasing focal or diffuse lymphocytic or plasma cellular infiltration of the thyroid, formation of lymphocytic follicles; final stage: fibrosis and disappearance of goiter parenchyma.</td>
<td>Hashimoto's thyroiditis</td>
</tr>
<tr>
<td>Neonatal goiter</td>
<td>Thyroid enlargement in the newborn, endemic in iodine-deficient areas.</td>
<td>Goiter in the new-born</td>
</tr>
</tbody>
</table>

**Differential diagnosis of thyroid enlargement**

The main cause for the diffuse goiter is an alimentary iodine deficiency situation in industrialized countries. A consequence of this is a TSH-independent adaptive response in the form of hyperplasia. If there is an enlarged thyroid gland, you have to think about a differential diagnosis should include:

- Diffuse goiter parenchymatosa;
- Hypertrophic Hashimoto's thyroiditis;
- Graves' disease;
- De Quervain's thyroiditis;
- Invasive sclerosing thyroiditis (“Riedel's thyroiditis”);
- Amyloidosis;
- Acromegaly.

**Differential diagnosis of euthyroid nodular goiter**

After noting an euthyroid nodular goiter, possible malignant and inflammatory changes, as well as functional autonomies, have to be excluded. It should be included in the differential diagnosis in case of:

- Graves' disease
- Functional autonomy (focal or disseminated)
- Malignant tissue changes (thyroid cancer)
- Hashimoto's thyroiditis
Laboratory diagnosis of nodular and multinodular goiter

For the avoidance of medullary thyroid carcinoma (MTC), the determination of thyroid autoantibodies is recommended via sonographic examination of:

- Thyroid peroxidase antibodies (TPO antibodies) and
- TSH receptor antibodies (TRAB).

Other laboratory parameters to check the thyroid function are:

- Free Triiodothyronine (T3);
- Free Thyroxine (T4);
- Thyroid-stimulating hormone (TSH);
- Thyroid releasing hormone test (TRH test);
- Microscopic antibodies (MAbs);
- Thyroglobulin antibodies (TgAb).

Differential diagnosis of multinodular goiter

A particular challenge in the differential diagnosis of thyroid disease is a multinodular goiter. By means of ultrasonography and scintigraphy, you should be able to identify suspicious focal or disseminated autonomies (a cold/hot node) and make further analysis. The aim of an examination is the detection or exclusion of thyroid autonomy.

If conspicuous nodes are detected by scintigraphy, they would require further clarification, which, in turn, should take place by means of fine-needle biopsy. The main purpose of the fine-needle biopsy, in this case, is the selection of thyroid nodules for the earliest possible histological evaluation of clinically normal or malignant tumors.
Differential Diagnosis of Throat Swelling

Not every throat swelling should be regarded automatically as a goiter. Goiter is abnormal swelling of the thyroid gland only with a definite underlying cause. A throat swelling can also occur as part of an increase in the volume of parathyroid glands, salivary glands, lymph nodes and the skin, the blood vessels, the muscles or the skeletal system. The differential diagnosis takes the following specific causes into consideration:

<table>
<thead>
<tr>
<th>Possible Disease</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goiter</td>
<td>Frequently</td>
</tr>
<tr>
<td>Lymphadenopathy due to infections, sarcoidosis, lymphadenitis, etc.</td>
<td>Very often</td>
</tr>
<tr>
<td>Salivary gland swelling (tumor/stone/inflammation)</td>
<td>Less common</td>
</tr>
<tr>
<td>Thrombosis or tumor-related superior vena cava syndrome</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

Management of Goiter

Treatment of individual goiter forms

The treatment of goiter is required only in case of complaints, a proven thyroid autonomy or well-secured malignancy. Initially, the motto “wait and watch” should be applied to asymptomatic patients. However, if waiting is contraindicated, there is a possibility of drug therapy *(levothyroxine, iodide)*.

In addition, radiiodine therapy or surgical therapy may be considered. In some cases, radioactive iodine is used to treat an overactive thyroid gland which results in the destruction of thyroid cells.

Having said that, each therapeutic procedure should be reviewed in terms of its suitability prior to taking action. Thus, the majority of patients with a nodule would first require no treatment, whereas, the treatment with malignancy is unquestionable. The thyroid surgery is obligatory for malignancy!

In the case of euthyroid diffuse goiter iodine deficiency is the main cause. Thus, the goal of any treatment should be the correction of iodine deficiency.

In the case of retrosternal or mediastinal goiter expansion, with the impairment of adjacent organs of the respiratory and digestive tract, a thyroidectomy in the affected region should be considered.

Prevention of goiter

Goiter prevention is largely influenced by its specific etiology. Preventive measures may include:

1. Correction of iodine deficiency and avoidance of dietary goitrogens. This is achieved through intake of iodine supplemented foods more often.
2. Careful use of levothyroxine combined with anti-inflammatory medication therapy plays a vital role in the prevention and reduction of goiters due to autoimmune thyroiditis.
3. Use of levothyroxine in patients with a previous diagnosis of nodular hyperplasia who have had a lobectomy, prevent its subsequent development in the contralateral lobe.
4. In the case of newborns screened for positive congenital hypothyroidism. Controlled use of levothyroxine during the postpartum period greatly reduces risks involved with congenital goiters due to inborn errors of metabolism.

Important to Remember

- Goiter is a **symptom**, not a disease.
- Initially, it indicates the **enlargement of the thyroid gland**.
- Rough **classification** of goiter: **diffuse** and **nodular goiter types**.

In case of a goiter suspicion, you should always exclude a possibly present malignancy.

**Evidence of a goiter** include:

- Thyroid enlargement;
- Nodules under the palpating fingers;
- Dysphagia;
- **Dyspnea**;
- Hoarseness;
- Difficulty swallowing, etc.

The examination of the eventually degenerated thyroid tissues occurs via **ultrasonography**, **scintigraphy**, and **fine-needle biopsy**.

In addition to goiter, further possible changes in the neck should be taken into consideration when a throat swelling is present. They may indicate entirely different diseases, such as swollen lymph nodes or the increase in the volume of salivary glands.

Review Questions

The answers are below the references.

1. **A lack of iodine cannot result in:**
   - A. lowering of thyroid stimulating hormone (TSH) plasma concentration.
   - B. reduction of triiodothyronine plasma concentration.
   - C. thyroid enlargement (goiter).
   - D. growth failure.
   - E. disturbances of intellectual development.

2. **Triiodothyronine (T3) and thyroxine (T4) hormones are formed in the thyroid. The precursor of these hormones is deposited extracellularly in the follicles from which the finished thyroid hormones are released by intracellular proteolysis. What is located in the follicles of the thyroid gland?**
   - A. Thyroglobulin
   - B. Thyrotropin-releasing hormone (TRH)
   - C. Iodate
   - D. Thyroxine-binding globulin
   - E. Transthyretin

3. **Disorders in the synthesis of thyroid hormones and regulation of the thyroid function are associated with a variety of symptoms in children and adults. Hyperthyroidism can be caused by autoantibodies that are bound to receptors with the thyroid epithelial cells. Which receptors are activated by these autoantibodies?**
   - A. Somatostatin
B. Thyreocalcitonin
C. Thyroid-stimulating hormone (TSH)
D. Thyreostatin
E. Thyroliberin (TRH)

References


Correct answers: 1A, 2A, 3C

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